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DRUGS THAT SUPPRESS TSH OR CAUSE CENTRAL HYPOTHYROIDISM

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Abstract

Many different drugs affect thyroid function. Most of these drugs act at the level of the thyroid in patients with normal thyroid function, or at the level of thyroid hormone absorption or metabolism in patients requiring exogenous levothyroxine. A small subset of medications including glucocorticoids, dopamine agonists, somatostatin analogs and rexinoids affect thyroid function through suppression of TSH in the thyrotrope or hypothalamus. Fortunately, most of these medications do not cause clinically evident central hypothyroidism. A newer class of nuclear hormone receptors agonists, called rexinoids, cause clinically significant central hypothyroidism in most patients and dopamine agonists may exacerbate ‘hypothyroidism’ in patients with nonthyroidal illness. In this review, we explore mechanisms governing TSH suppression of these drugs and the clinical relevance of these effects.

Keywords

TSH; Central hypothyroidism; Medications; Thyroid function; Glucocorticoids; Dopamine; Somatostatin; Rexinoids

Introduction

Many drugs and medications can affect thyroid function. Thyroid hormone levels can be altered by drugs at many levels including the hypothalamus, thyrotropes in the anterior pituitary gland,

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Clinical Practice Points

Most drugs that suppress serum TSH (glucocorticoids, dopamine agonists, somatostatin analogs) do not cause clinically significant hypothyroidism

Metformin may affect thyroid function tests and TSH levels in patients on exogenous levothyroxine. Monitoring of TSH and free T4 levels is advised for patients taking both metformin and levothyroxine.

Rexinoids, which are used in certain cancers, suppress serum TSH in most patients and cause clinically significant central hypothyroidism. Careful monitoring of TSH and free T4 levels is important.

Research agenda

More studies are needed to define the extent and mechanism of how metformin may affect serum TSH and thyroid function tests in patients on both metformin and levothyroxine

Newer generation rexinoids may be used to suppress serum TSH in certain populations (thyroid cancer patients, thyroid hormone resistance, TSH-secreting pituitary tumors), but side-effects (hypertriglyceridemia, white blood cell count suppression) need to be lower than seen with the currently approved rexinoid bexarotene

synthesis and secretion from the thyroid gland and metabolism of thyroid hormones through deiodination, sulfation and glucuronidation (1). Drugs may also affect thyroid hormone levels by altering affinity for or levels of thyroxine binding globulin. Finally, drugs may affect absorption of thyroid hormone in patients who are dependent on exogenous levothyroxine (2). Table 1 shows drugs that affect patients with an intact hypothalamic-pituitary-thyroid axis which is subdivided by known mechanism of action. Table 2 is a list of medications and drugs that affect patients who are dependent on exogenous levothyroxine.

Drugs that affect TSH or thyroid function at the level of the hypothalamus or pituitary are only a small subset of drugs that can affect thyroid function, and these drugs will be the focus of this review.

Drugs that suppress serum TSH levels

Glucocorticoids

Glucocorticoids have long been known to affect serum TSH levels in humans (3;4). Physiologic levels of hydrocortisone appear to play an important role in the diurnal variation of serum TSH levels with lower levels in the morning and higher levels at night (5;6). Wilber and Utiger showed that high dose glucocorticoids suppressed serum TSH in hypothyroid patients and normal subjects (3). This effect appeared to involve TSH secretion and was controlled at the level of the hypothalamus. Others have confirmed this effect, but long-term high dose glucocorticoids or Cushing's syndrome cortisol excess do not appear to cause clinically evident central hypothyroidism requiring thyroid hormone replacement (4;7). Dexamethasone doses as low as 0.5 mg can lower serum TSH levels, while 30 mg of prednisone is likely required to significantly alter TSH levels (4). Glucocorticoids appear to suppress release of TSH from thyrotropes in a PKC-dependent manner through the protein annexin 1 (8). The effect of glucocorticoids on TSH secretion is likely through inhibition of TRH in the hypothalamus. Glucocorticoid receptors are found in the TRH neurons of the PVN and a glucocorticoid response element has been identified on the TRH gene (9). Alkemade and colleagues have more recently shown that high dose glucocorticoids decrease TRH mRNA levels in the human hypothalamus, which is likely the primary mechanism for lower TSH secretion from the pituitary (10).

In summary, glucocorticoids can lower serum TSH levels and decrease TSH secretion through direct effects on TRH in the hypothalamus. Chronic high dose glucocorticoids or severe Cushing's syndrome do not appear to cause clinically significant central hypothyroidism.

Dopamine/bromocryptine

Dopamine used in critical illness and the dopamine agonist bromocryptine used for disorders like hyperprolactinemia can suppress serum TSH. Bromocryptine has been shown to reduce serum TSH in patients with selective pituitary resistance to thyroid hormone (11).

Dopamine exerts its effect on the hypothalamic-pituitary-thyroid axis through the activation of dopamine D2 receptors (D2R), but appears to have opposite effects on the hypothalamus and the pituitary thyrotrope. Dopamine infusions in healthy volunteers reduces TSH pulse amplitude without significantly altering TSH pulse frequency (12;13). Bromocryptine appears to have the same effect on TSH pulse amplitude and is likely occurring through the same D2R mechanism (14). Interestingly, dopamine stimulates release of TRH from rat hypothalamus through the same D2R (15), but the overall effect of dopamine is to lower serum TSH so this direct stimulatory effect on the hypothalamus cannot override the inhibitory effect of dopamine on the pituitary. Prolonged treatment with bromocryptine does not appear to cause central hypothyroidism since many patients treated with bromocryptine for macroprolactinomas actually have resolution of central hypothyroidism caused by the adenoma (16). Studies using

dopamine infusions in critically ill adults and neonates with the nonthyroidal illness (NTI) syndrome suggest that dopamine and NTI have an additive effect of HPT axis suppression. This may lead to iatrogenic central hypothyroidism in these patients (17;18). It is not clear whether treatment with levothyroxine is indicated in patients with NTI who are receiving dopamine infusions.

Somatostatin analogs

Somatostatin binds to 5 different extracellular receptors on pituitary cells to inhibit hormone secretion through adenylate cyclase signaling, calcium flux and cell polarization (19). Analogs of somatostatin are an effective medical therapy in patients with the syndrome of pituitary resistance to thyroid hormone (20) or TSH-secreting pituitary tumors that cannot be adequately controlled with surgery (21). Administration of somatostatin to healthy volunteers decreased both pulse amplitude and pulse frequency of serum TSH during frequent blood sampling (13). This is at least in part through direct inhibition of TSH secretion from pituitary thyrotropes (22;23). Long-acting somatostatin analogs suppress serum TSH and blunt TRH-stimulated TSH levels in healthy volunteers (24), while chronic nocturnal octreotide therapy in children treated for tall stature reduces nocturnal levels of serum TSH without affecting serum thyroxine concentrations (25). A one year study of continuous octreotide infusion as therapy to prevent retinopathy in diabetes, showed that TSH levels were modestly suppressed, but these patients did not have clinically significant central hypothyroidism (26). Acromegalics treated with octreotide for one month demonstrated lower serum TSH and blunted TRH-stimulated levels, but continued treatment for 6 months had no effect on basal TSH levels or serum T4 levels (27). Interestingly, serum T3 levels remained lower and TRH-stimulated TSH levels were blunted after 6 months of therapy. Another study also showed lower serum T3 levels in acromegalic patients treated with octreotide, which was associated with higher reverse T3 levels, suggesting that octreotide therapy may directly or indirectly affect thyroid hormone metabolism (28). In summary, somatostatin analogs suppress serum TSH likely through direct effects on pituitary thyrotropes, but these effects are primarily transient and do not appear to cause clinically significant central hypothyroidism.

Rexinoids

Rexinoids are a subclass of vitamin A derivative drugs, or retinoids, that interact with a specific nuclear hormone receptor, the retinoid X receptor (RXR). RXR forms a protein partner, or heterodimer, with other nuclear transcription factors, including thyroid hormone receptor (TR), retinoic acid receptor (RAR), vitamin D receptor (VDR), peroxisome proliferator-activated receptor (PPAR) and liver X receptor among others. These heterodimer partners can influence transcription of many different target genes through ligand activation of either RXR or its protein partner. Bexarotene (Targretin®) is the only rexinoid currently approved for clinical use, primarily for treatment of cutaneous T cell lymphoma (29). Bexarotene and other 'second-generation' rexinoids are currently being studied as therapies for other advanced malignancies including lung, breast and thyroid (30;31). Furthermore, rexinoids may be useful therapies for certain metabolic disorders including diabetes and obesity (32-34).

Case study—A 76 year-old male with a diagnosis of cutaneous T cell lymphoma presented for enrollment into an open label study of oral bexarotene after failing multiple topical and systemic therapies (35). Within two weeks of starting bexarotene (650 mg/m²/day) the patient developed symptoms of hypothyroidism including cold intolerance, fatigue and depression. He was noted to have low serum T4 and T3 levels consistent with hypothyroidism, but his serum TSH was also suppressed. The bexarotene was discontinued; his thyroid function tests normalized and symptoms resolved.

A subsequent study was conducted on 27 patients being treated with bexarotene for cutaneous T cell lymphoma which demonstrated significant reversible TSH suppression below the lower limit of the reference range in 26/27 subjects and clinical symptoms or signs of hypothyroidism in 19 patients (35). We also demonstrated that another synthetic rexinoid (LG346) suppressed TSH β promoter activity in thyrotrope cells, suggesting a direct suppression on gene transcription.

Single dose rexinoid was subsequently shown to suppress TSH levels in rats (36), but the only data in humans was patients with advanced cancer. We therefore conducted a randomized, blinded, placebo-controlled, cross-over study to determine if single dose bexarotene could suppress TSH in healthy volunteers (37). Bexarotene rapidly and significantly suppressed serum TSH, but had no effect on prolactin or cortisol levels, suggesting this was a specific effect on thyrotropes. We subsequently confirmed this effect in mice using a second-generation rexinoid and showed that the effect is primarily through direct suppression of transcription of the TSH β subunit gene (unpublished data), since the rexinoid did not decrease TRH mRNA in the hypothalamus (38). Our group and others have also shown that rexinoids likely affect thyroid hormone metabolism as well through deiodination, sulfation and possibly glucuronidation (39). Figure 1 is a summary of the proposed mechanisms by which rexinoids cause clinically significant central hypothyroidism.

Other medications that may affect TSH levels

Certain antiepileptic medications including carbamazepine, oxcarbamazepine and valproic acid increase metabolism of thyroid hormones through the hepatic P450 system, but may also alter pituitary responsiveness to hormonal feedback and cause central hypothyroidism (40; 41). Other investigators have shown that the hypothalamic-pituitary axis is not affected by these medications and a specific mechanism has not been identified (42;43), so it remains controversial if these drugs affect thyrotrope function and serum TSH levels in humans.

Recent observational studies have suggested that metformin can lower serum TSH levels (44). One study demonstrated this effect only in type 2 diabetics who also had hypothyroidism, but not in patients with normal thyroid function (45). This effect may be through altered free T4 levels in patients who are hypothyroid (46), but the exact mechanism is not known.

Summary

Many drugs and medications can affect thyroid function, but only a small subset (glucocorticoids, dopamine agonists, somatostatin analogs and rexinoids) suppress TSH at the level of the hypothalamus or pituitary. Fortunately, the widely used glucocorticoids and the somatostatin analogs do not induce clinically evident central hypothyroidism even after prolonged high dose use. Dopamine agonists do not cause clinically significant central hypothyroidism, but may have an additive effect of TSH suppression in patients with nonthyroidal illness, which may lead to a state of iatrogenic central hypothyroidism in this patient population. Rexinoids, clearly induce clinically significant central hypothyroidism in most patients, who require levothyroxine replacement and monitoring of serum free T4 levels. As this newer class of drugs may be used in more patients (advanced cancer, metabolic disorders, dermatologic disorders), clinicians need to be aware of this unique and treatable side-effect.

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Effects of Rexinoids on the Hypothalamic-Pituitary-Thyroid Axis

Figure 1.

Table 1
Drugs known to affect thyroid function in patients with an intact hypothalamic-pituitary-thyroid axis. Mechanism of action in *italics*

Inhibition of T4/T3 synthesis

Propylthiouracil

Methimazole

Inhibition of T4/T3 secretion *

Lithium

Iodide

Amiodarone

Aminoglutethimide

Thyroiditis

Interferon

Interleukin-2

Amiodarone

Sunitinib **

Jod-Basedow Hyperthyroidism

Iodide

Amiodarone

TSH suppression

Glucocorticoids

Dopamine agonists

Somatostatin analogs

Rexinoids

Carbamazepine/Oxcarbazepine[?]

Metformin[?]

TSH elevation

Metyrapone

Displacement from thyroxine binding globulin (laboratory artifact)

Furosemide

Phenytoin

Probenecid

Heparin

Nonsteroidal anti-inflammatory medications

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* - exacerbated by underlying lymphocytic thyroiditis

** - may be through thyroid gland atrophy and not thyroiditis

? - not verified by multiple studies/investigators

Table 2
Drugs that affect thyroid function in patients taking levothyroxine. Mechanism of action in *italics*

Inhibition of levothyroxine absorption

Iron
 Calcium
 Aluminum hydroxide
 Colestyramine
 Colestipol
 Sucralfate
 Raloxifene

Increased hepatic metabolism

Phenobarbitol
 Phenytoin
 Carbamazepine
 Rifampin
 TKI (Imatinib, axitinib, motesanib, vandetanib)
 Rexinoids

Decrease hepatic metabolism

Metformin[?]

Inhibition of 5' deiodinase

Propylthiouracil
 Methimazole
 Propranolol
 Glucocorticoids
 Iodide

Increased thyroxine binding globulin levels

Estrogen
 Raloxifene
 Tamoxifen
 Methadone
 Mitotane
 Fluorouracil

Decreased thyroxine binding globulin levels

Androgens
 Glucocorticoids
 Nicotinic acid

TKI - tyrosine kinase inhibitors

[?]

- not verified by multiple studies/investigators

Table 3
Drugs that suppress TSH and proposed mechanisms of action

<u>Drug class</u>	<u>Mechanism of action</u>	<u>Clinically significant hypothyroidism</u>
Glucocorticoids	Activation of GR Inhibition of TRH synthesis/ secretion	No
Dopamine agonists	Activation of D2 receptors on thyrotropes Reduced TSH pulse amplitude	Probably not May cause hypothyroidism in pts with NTI
Somatostatin analogs	Activation of SSTR in thyrotropes Inhibition of TSH secretion Altered thyroid hormone metabolism?	No
Rexinoids	Activation of RXR Inhibition of TSH β transcription in the pituitary Increased peripheral metabolism of thyroid hormone	Yes

GR - glucocorticoid receptor

D2 - dopamine receptor, type 2

SSTR - somatostatin receptor

RXR - retinoid X receptor